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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,422	06/26/2003	David F. McComsey	ORT-1222 USA DIV	6306

27777 7590 08/10/2005

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/606,422	MCCOMSEY ET AL.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 5/23/05, claims 10-17 have been cancelled, and claims 18-26 added. Claims 18-26 are now pending.

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-26 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have provided data (page 9+) which indicates that some binding to a thrombin receptor occurs with several of the claimed compounds. Presumably this was assessed by displacement of Ser-(pF)Phe-Har-Leu-Har-Lys-Tyr-NH_2 from "CHRF" membranes. Applicants have also shown inhibition of thrombin-induced platelet aggregation. Based on this, the examiner will stipulate that inhibition of platelet aggregation will occur within a mammal, and that thrombin receptor binding will occur *in vivo* as well. However, these experiments are not tantamount to a showing of therapeutic efficacy. Even if platelet aggregation is mitigated to some extent, it does not follow therefrom that there exists any disease for which benefit will accrue to the

patient who is afflicted with excess platelet aggregation. First, the excess platelet aggregation may not be the sole cause of the disease to begin with, and second, there is no assurance that the extent of the inhibition will be sufficient to overcome the adverse effects of the disease. It is recognized also the the thrombin receptor is involved in a diverse array of biochemical processes. However, it is not evident that success at treating a human disease has ever been achieved with a thrombin receptor antagonist, and even if some success has been achieved in this regard, the assumption would be that the claimed compounds are not as effective at antagonizing the thrombin receptor as that of the prior art compounds. In addition there is the matter of bioavailability and pharmacokinetics, which are likely to be different between compounds.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, one cannot "predict" therapeutic efficacy in the treatment of thrombin-mediated disorders based solely on the observation that a compound can bind to the thrombin receptor, or inhibit platelet aggregation. "Undue experimentation" would be required to practice the claimed

invention.

In addition to the foregoing, there is the matter of "modulation". Claim 18 could be interpreted to mean that the compounds of formula (1) can "modulate" the thrombin receptor. The term "modulate" would imply both an antagonism and an activation of the receptor. While it may be that one or the other can be achieved, it is far from apparent how applicants intent to simultaneously antagonize and activate the receptor.

The claims encompass treatment of neurodegenerative diseases. Neurodegenerative diseases encompass the following:

> AIDS Dementia Complex (a.k.a. HIV-Associated Dementia) Amyotrophic Lateral Sclerosis (a.k.a. Lou Gehrig's Disease), Alzheimer 's Disease, Huntington's Disease, Multiple Sclerosis, Parkinson's Disease, Creutzfeldt-Jakob disease, progressive supranuclear palsy, Creutzfeldt-Jakob disease, multifocal leukoencephalopathy, diffuse and transitional Lewy body disease, frontotemporal degeneration, corticobasal degeneration, multiple system atrophy, Pick Disease, argyrophilic grain disease and corticobasal degeneration. In addition, experimental automimmune encephalomyelitis is an animal model of multiple sclerosis.

Applicants have not shown how the skilled artisan can use the compounds to treat any of these.

In response to the foregoing, applicants have argued that during the prosecution of application 09/565715, the examiner imposed, and subsequently withdrew an enablement rejection against one or more claims. Applicants have further argued that because the examiner withdrew an enablement rejection that had been imposed in another application, he

is barred from imposing an enablement rejection in the instant case. First, as a general proposition, applicants are incorrect, as a matter of law, and as a matter of Patent Office procedure. Merely because an examiner has undertaken a given course of action in one application does not mean that an examiner must take the same course of action in a different application. In any event, however, the point is moot. The claims which were allowed in application 09/565715 were drawn to compounds, and there were no therapeutic method claims. Nor was there even an allowed claim drawn to a "pharmaceutical" composition. Accordingly, the enablement issues in the instant application are not relevant to those in the instant application.

It may be the case that applicants have shown that some of the compounds (to which the claims are directed) can bind to a thrombin receptor. However, it remains to be determined whether this binding results in antagonism of the receptor, or activation. And even if, at some point in the future, applicants are both willing and able to make this determination, it will not follow therefrom that the skilled pharmacologist will be able to draw any conclusions therefrom with regard to physiological activity in diseased mammals. Consider the following:

- Torsello, Antonio (*Endocrinology* **143** (5) 1968, 2002) pertains to growth hormone, and discloses that stimulation of the growth hormone secretagogue receptor does not correlate with capability to stimulate GH secretion.

- McFadyen "Modifications of the cyclic mu receptor selective tetrapeptide Tyr-c[D-Cys-Phe-D-Pen]NH(Et): effects on opioid receptor binding and activation"

(*Journal of Peptide Research* (2000 Mar) **55** (3) 255-61) reported on modifications to the title peptide. The reference discloses that potency changes did not always correlate with affinity, suggesting that the conformation required for binding and the conformation required for activation of the opioid receptors are different.

- Keith , "mu-Opioid receptor internalization: opiate drugs have differential effects on a conserved endocytic mechanism in vitro and in the mammalian brain" (*Molecular Pharmacology* **53** (3) 377-84, 1998) discloses that the different effects of individual agonists are not correlated with their potencies for receptor activation and that a variety of clinically important agonists differ significantly in their relative abilities to stimulate the rapid internalization of opioid receptors.

- Xiao (*Biochemistry* 40, 2860, 2001) has looked at the relationship between cAMP production in cells, and in vivo activity. While some degree of correlation was noted, a 1:1 correspondence was absent. As stated on page 2864, col 2, "the results indicated that these functions may be dissociated, mostly likely to additional determinantants of in vivo activity...". For example, as conveyed in table 6, Phe'-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 along with decreased in vivo insulinotropic activity; by contrast, Acetyl-GLP-1 exhibited decreased receptor activation compared with WT GLP-1 accompanied by an increase in in vivo insulinotropic activity. Thus, receptor activation is not necessarily predictive of in vivo activity.

- Lunec, "MSH receptor expression and the relationship to melanogenesis and metastatic activity in B16 melanoma" (*Melanoma Research* (1992 May) **2** (1) 5-12) compared the effects of different pro-opiomelanocortin (POMC) peptides on melanogenesis and metastasis and their relationship to MSH receptor expression in B16F1 melanoma cells. The authors disclose that the relative binding affinities of the different peptides, measured by displacement of [^{125}I]-Nle^{4}-D-Phe^{7}-alpha-MSH, did not closely correlate with the relative potencies in stimulating melanogenesis and metastasis. This suggests that receptor activation and the subsequent biological response is not determined solely by binding affinity.

In accordance with the foregoing, it is clear that whether one is endeavoring to stimulate a receptor in vitro or to antagonize a receptor *in vitro*, extrapolating to a therapeutic method leads to "unpredictable" results.

Although applicants have not yet done so, applicants may, at some point in the future, provide a reference which shows that a monoclonal antibody to one of the thrombin receptors has shown some promise in an animal model of a disease. Should this event come to pass, one of the arguments which will be advanced by the examiner is that, when using Mab's, there is often a a very narrow "window of opportunity" during which one can create the appearance of therapeutic efficacy. This issue is discussed, e.g., in Jabs (*Cellular immunology* 154, 66-76, 1994) and in Beilharz (*J Immunol* 172, 4917-25, 2004). Neither Jabs nor Beilharz mentions MAb's to a thrombin receptor, but they do discuss the use of MAb's in the treatment of disease; they also report that failure generally occurs, with the exception of one or two specific time points (before or after onset of the disease). Thus, use of MAb's in treatment of disease leads to "unpredictable" results. Then there is the issue of multiple thrombin receptors (PAR1, PAR2, etc.); applicants have not determined which of these should be antagonized (or activated). An additional point with regard to MAb's is that applicants have asserted (page 1, line 32+, specification) that many of the compounds (to which the instant claims are directed) are not antagonists, but rather are activators of one of the thrombin receptors. Thus, applicants have provided

no guidance as to which compounds will antagonize one of the thrombin receptors (and if so, which receptor), and which compounds will activate one of the thrombin receptors (and if so, which receptor).

Thus, guidance is lacking with respect to the question of "how to use" the compounds; and there are no working examples which show the skilled artisan how to use the compounds in accordance with the claimed invention. In addition, there is no evidence that the prior art shows the skilled artisan how to use the compounds. And given the high degree of "unpredictability" in pharmacology, the skilled artisan would conclude that "undue experimentation" would be required to practice the claimed invention.

✧

Claims 18- 26 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 18 recites "treating a condition mediated by modulation of the thrombin receptor". This renders the claim indefinite as to whether the condition *per se* is mediated by modulation of the receptor, or whether it is the treatment that is mediated by modulation of the receptor. There are multiple ways of interpreting the claim, including the following:

  A method of treating a condition that is exacerbated by antagonizing the thrombin receptor

  A method of treating a condition that is ameliorated by antagonizing the thrombin receptor

  A method of treating a condition that is exacerbated by activating the thrombin receptor

A method of treating a condition that is ameliorated by activating the thrombin receptor

Which of these are intended?

- Claim 18 makes reference to a "formula 1". However, there is no formula 1 provided in the claim. What is provided is a formula I (Roman numeral I). See also claim 26.

- Claim 22 is drawn to a method, and is dependent on claim 18. Claim 22 recites the following: "administering ...the compound of claim 18".
This phrase implies that claim 18 is drawn to a compound; however, this is not the case. Claim 18 is drawn to a method, thus generating an inconsistency. It is suggested that claim 22 be cast in independent form.

✧

With regard to the IDS filed 8/7/03, applicants are advised that application 09/565715 remains unavailable at this time (7/26/05).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at (571)272-0974. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800